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EXAMINER
FORMAN, BETTY J

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/784,866	EMPEDOCLES ET AL.	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-25 and 28-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-25 and 28-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to papers filed 1 July 2002 in Paper No. 10 in which claims 1, 4, 10, 22, 25, 28-33, 37 and 38 were amended and claims 26 and 27 were canceled and papers filed 21 November 2002 in Paper No. 14 in which claims 1-3, 5-7, 10, 22, 29-33 and 37 were amended, claim 4 was canceled and claims 40-51 were added. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No. 7 dated 1 February 2002 are withdrawn in view of the amendments. All of the arguments have been thoroughly reviewed but are deemed moot in view of the amendments, withdrawn rejections and new grounds for rejection. The arguments are addressed as they apply to the new grounds for rejection. New grounds for rejection are discussed.

Claims 1-3, 5-25, 28-51 are under prosecution.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-28, 31, 40, 41, 43 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-28, 40, 41 and 47 are indefinite in Claim 1 because the claim is drawn to a method for counting a single copy of a target but the claim does not recite a method step of counting. Therefore it is unclear whether the method accomplishes the claimed purpose.

Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

b. Claim 15 is indefinite for the recitation "said first affinity moiety" because the recitation lacks proper antecedent basis in Claim 1. It is suggested that Claim 1 be amended to provide proper antecedent basis.

c. Claims 31 and 43 are indefinite in Claim 31 for the recitations "said first quantum dot" and "said second quantum dot" because the recitations lack proper antecedent basis in the claim. It is suggested that the claim be amended to provide proper antecedent basis.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-3, 5-18, 23, 29, and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Bruchez et al (U.S. Patent No. 6,274,323 B1, filed 5 May 2000).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding Claim 1, Bruchez et al disclose a method of counting the presence of a single copy of a target species in a sample the method comprising detecting an optical characteristic of a first and second quantum dot attached to said single copy wherein said single copy is bound to an affinity moiety for said immobilized target species said first and second quantum dot are distinguishable thereby detecting said single copy of the target (Abstract, Column 16, lines 1-6, and Column 36, line 14-Column 37, line 44 and Fig. 1). It is noted that the claims do not recite a method step for counting. However, Bruchez et al detect a single target and thereby count the single target as "one" target (Abstract and Column 16, lines 1-6).

Regarding Claim 2, Bruchez et al disclose the method wherein the first and second quantum dot are attached to the target prior to binding to the affinity moiety (Column 7, lines 36-65).

Regarding Claim 3, Bruchez et al disclose the method wherein the first and second quantum dot are attached to the target after binding to the affinity moiety (Fig. 1).

Regarding Claim 5, Bruchez et al disclose the method wherein the binding of the target to affinity moiety forms a complex that is detected by fluorescence from both first and second dot (Claim 9).

Regarding Claim 6, Bruchez et al disclose the method wherein the quantum dots are distinguishable by an optical characteristic selected from fluorescence spectrum, fluorescence emission, fluorescence excitation, uv absorbance visible light absorbance, fluorescence quantum yields fluorescence lifetime and light scattering (Column 9, lines 37-56).

Regarding Claim 7, Bruchez et al disclose the method wherein the first and second dots are visually distinguishable as a first and second color (Column 20, lines 8-44).

Regarding Claim 8, Bruchez et al disclose the method wherein the first and second color combine to form a third color that is distinguishable (Column 20, lines 8-44).

Regarding Claim 9, Bruchez et al disclose the method wherein the target species ha n quantum dots attached thereto and each of said n quantum dots is distinguishable from each other and n is an integer from 3 to 10 (Column 19, lines 45-67).

Regarding Claim 10, Bruchez et al disclose the method wherein said target moiety is selected from the group consisting of antibodies, aptamers, proteins, streptavidin, nucleic acids, and biotin (Column 6, lines 48-57 and Column 7, line 66-Column 8, line 9).

Regarding Claim 11, Bruchez et al disclose the method wherein the affinity moiety is labeled with a quantum dot e.g. antibody (Fig. 1).

Regarding Claim 12, Bruchez et al disclose the method wherein the target species is selected from the group consisting of biomolecules and bioactive molecules (Column 6, lines 48-57 and Column 7, line 66-Column 8, line 9).

Regarding Claim 13, Bruchez et al disclose the method wherein the affinity moiety is selected from the group consisting of biomolecules and bioactive molecules (Column 6, lines 48-57 and Column 7, line 66-Column 8, line 9).

Regarding Claim 14, Bruchez et al disclose the method wherein the substrate has bound thereto a second affinity moiety i.e. antibody (Fig. 1A).

Regarding Claim 15, Bruchez et al disclose the method wherein the first and second affinity moieties are different i.e. primary and secondary antibodies (Column 38,line 59-Column 39, line 19 and Fig. 1A).

Regarding Claim 16, Bruchez et al disclose the method wherein said substrate has bound thereto m affinity moieties and m is an integer from 1 to 10,000 (Column 38, lines 52-65).

Regarding Claim 17, Bruchez et al disclose the method wherein each of said affinity moieties are different (Column 38, lines 52-58).

Regarding Claim 18, Bruchez et al disclose the method wherein said affinity moieties are ordered in an array format (Column 38, lines 59-65).

Regarding Claim 23, Bruchez et al disclose the method wherein the substrate is a microtitre plate (Column 38, lines 59-65).

Regarding Claim 29, Bruchez et al disclose a method of counting a single copy of a target species in solution the method comprising detecting a single copy of said target by detecting essentially simultaneously an optical characteristic of a first quantum dot of a first color and second quantum dot or a second color attached to said single copy wherein said first and second quantum dot are distinguishably different colors thereby detecting said single copy of the target (Abstract, Column 41, lines 10-48 and Fig. 1C). Burchez et al disclose the method detects a single copy of a target (Column 16, lines 1-6) and by detecting a single copy they thereby count as one the single copy.

Regarding Claim 30, Bruchez et al disclose a method of counting a single copy of a target immobilized on a substrate wherein the target is a member of a population immobilized on the substrate the method comprising detecting a single copy of said target by detecting an optical characteristic of a first and second quantum dot attached to said single copy wherein the single copy is bound to an affinity moiety immobilized on a substrate wherein said first and second quantum dot are distinguishable (Column 38, line 52-Column 39, line 24) and detecting is performed with a means having a resolution higher than spacing between the member populations (Column 19, lines 32-44).

6. Claims 1, 3, 5-8, 10-13, 41 and 42 are rejected under 35 U.S.C. 102(e) as being anticipated by Weiss et al (U.S. Patent No. 6,207,392 B1, filed 1 March 1999).

Regarding Claim 1, Weiss et al disclose a method of counting the presence of a single copy of a target species (i.e. detectable substance, Column 4, lines 15-20, 28-35 and 54-56) in a sample comprising: detecting an optical characteristic of a first and second quantum dot attached to the single target species wherein the single target is bound to an affinity moiety immobilized on a substrate and wherein the first and second quantum dots are distinguishable (Column 12, lines 7-37) wherein detection of fluorescence in the sample detects the presence of one target i.e. the labeling is via bonding of the nucleic acid affinity molecule to its complementary sequence (Column 4, lines 27-67 and Claim 114).

Regarding Claim 3, Weiss et al disclose the method wherein the quantum dots are attached to the target after binding the target to the affinity moiety (Column 4, lines 27-67 and Claim 114).

Regarding Claim 5, Weiss et al disclose the method wherein binding of the target to affinity moiety forms a target species-affinity moiety complex that is detected by fluorescence form both first and second quantum dot attached to the complex (Column 18, line 57-Column 19, line 16).

Regarding Claim 6, Weiss et al disclose the method wherein the quantum dots are distinguishable by an optical characteristic selected from fluorescence spectrum, fluorescence emission, fluorescence excitation, uv absorbance visible light absorbance, fluorescence quantum yields fluorescence lifetime and light scattering (Column 18, line 57-Column 19, line 33).

Regarding Claim 7, Weiss et al disclose the method wherein the first and second quantum dot are visually distinguishable as a first and second color (Column 22, lines 24-48).

Regarding Claim 8, Weiss et al disclose the method wherein the first and second color combine to form a color distinguishable from the first and second color (Column 22, line 24-Columnn23, line 30).

Regarding Claim 10, Weiss et al disclose the method wherein the quantum dots are attached to a targeting moiety for the target species and the targeting moiety is selected from antibody, aptamer, protein, streptavidin, nucleic acids and biotin (Column 9, lines 14-35).

Regarding Claim 11, Weiss et al disclose the method wherein the affinity moiety is labeled with a quantum dot (Column 9, lines 14-18).

Regarding Claim 12, Weiss et al disclose the method wherein the target species is selected from a biomolecule and bioactive molecule (Column 6, lines 35-39).

Regarding Claim 13, Weiss et al disclose the method wherein the affinity moiety is selected from a biomolecule and bioactive molecule (Column 9, lines 14-35).

Regarding Claim 41, Weiss et al disclose teach the method wherein said optical characteristic of the quantum dot is detected by coincidence detection (Column 17, lines 11-31).

Regarding Claim 42, Weiss et al disclose the method wherein the optical characteristic is fluorescence (Column 18, line 57-Column 19, line 16).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-3, 5-7, 9-18, 29, 40-42, 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bawandi et al (U.S. Patent No. 6,306,610 B1, filed 17 September 1999) in view of Singer et al (U.S. Patent No. 5,866,331, issued 2 February 1999).

Regarding Claim 1, Bawandi et al disclose a method of detecting a target species immobilized on a substrate comprising: detecting a single copy of said target species by detecting fluorescence emitted by a quantum dot attached to said single copy, wherein said single copy is bound to an affinity moiety for said target species immobilized on said substrate (Column 22, lines 59-65) wherein said target species has distinguishable first and second quantum dot attached thereto i.e. probes labeled with two different quantum dots are attached to the nucleic acid target species via hybridization (Column 24, line 62-Column 25, line 17 and Fig. 3) but they do not specifically teach their method is for counting a single copy. However, single-copy counting was well known in the art at the time the claimed invention was made as taught by Singer et al who teach a similar method and they teach that single-copy counting is important for diagnosing viral nucleic acids e.g. HIV and genetic defects (Column 3, lines 17-21). The similar method of Singer et al comprises detecting an optical characteristic of a first and second label attached to said single copy wherein said first and second label are distinguishable thereby detecting said single copy of the target nucleic acid (Abstract, Column 1, lines 45-67 and Claim 1). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the single-copy counting of Singer et al to the method of Bawandi et al and to detect the first and second quantum dot attached to a single copy of a target species for the expected benefit of diagnosing clinically important conditions e.g. HIV and genetic defects as taught by Singer et al (Column 3, lines 17-21).

Regarding Claim 2, Bawandi et al disclose the method wherein said quantum dots are attached to said target species prior to binding said target species to said affinity moiety i.e. the

quantum dot is attached to the second antibody which is the target species immobilized to the substrate via binding to the antigen (Column 22, lines 59-65).

Regarding Claim 3, Bawandi et al disclose the method wherein said quantum dots are attached to said target species after binding said target species to said affinity moiety i.e. the quantum dot is attached to the second antibody which binds the antigen target species immobilized to the substrate (Column 22, lines 59-65).

Regarding Claim 5, Bawandi et al disclose the method wherein binding of said target species to said affinity moiety (i.e. probe) forms a target species-affinity moiety complex that is detected from both first and second quantum dots attached to said complex (Column 25, lines 11-16).

Regarding Claim 6, Bawandi et al disclose the method wherein said quantum dots are distinguishable by a characteristic which selected from fluorescence spectrum, fluorescence emission, ultraviolet light, visible light, light scattering and combinations thereof (Column 4, lines 7-56).

Regarding Claim 7, Bawandi et al disclose the method wherein said first and second dots are visually distinguishable as a first color and second color i.e. each have a distinct emission spectra (Column 4 lines 45-49).

Regarding Claim 9, Bawandi et al disclose the method wherein said target species has n quantum dots attached thereto, wherein each of said quantum dots is distinguishable from each other and wherein n is 3 (Column 16,lines 27-56).

Regarding Claim 10, Bawandi et al disclose the method wherein said first and second quantum dots are attached to a targeting moiety selected from the group consisting of antibodies, proteins, streptavidin, nucleic acids and biotin (Column 6, line 62-Column 7, line 7).

Regarding Claim 11, Bawandi et al disclose the method wherein said affinity moiety is labeled with a quantum dot (Column 22, lines 63-65).

Regarding Claim 12, Bawandi et al disclose the method wherein said target species is selected from the group consisting of organisms, biomolecules and bioactive molecules (Column 5, lines 6-8).

Regarding Claim 13, Bawandi et al disclose the method wherein said affinity moiety is selected from the group consisting of biomolecules and bioactive molecules (Column 6, line 62-Column 7, line 7).

Regarding Claim 14, Bawandi et al disclose the method wherein said substrate has bound thereto a second affinity moiety i.e. multiple antigen-specific antibodies are immobilized (Column 22, lines 59-61).

Regarding Claim 15, Bawandi et al disclose the method wherein said first and second moiety are different affinity moieties i.e. different antibody-specific antigens are immobilized on the substrate (Column 22, lines 59-61).

Regarding Claim 16, Bawandi et al disclose the method wherein said substrate has between 1 and 10,000 affinity moieties bound thereto i.e. their substrate for multiplexing has multiple (i.e. more than one) antibody-specific moieties (Column 22, lines 59-61). Therefore, their multiplexing substrate has between 1 and 10,000 moieties attached.

Regarding Claim 17, Bawandi et al disclose the method wherein each affinity moiety is different i.e. disparate antibody-specific antigens (Column 22, lines 62-63).

Regarding Claim 18, Bawandi et al disclose the method wherein m affinity moieties are ordered in an array format (Column 26, liens 12-41).

Regarding Claim 29, Bawandi et al disclose a method of detecting a target species in solution said method comprising: detecting a single copy of said target species by detecting essentially simultaneously fluorescence emitted by a first quantum dot of a first color attached to said single copy and a second quantum dot of a second color attached to said single copy wherein said first color and said second color are distinguishably different (Column 7, lines 5-27) but they do not specifically teach their method is for counting a single copy. However,

single-copy counting was well known in the art at the time the claimed invention was made as taught by Singer et al who teach a similar method and they teach that single-copy counting is important for diagnosing viral nucleic acids e.g. HIV and genetic defects (Column 3, lines 17-21). The similar method of Singer et al comprises detecting an optical characteristic of a first and second label attached to said single copy wherein said first and second label are distinguishable thereby detecting said single copy of the target nucleic acid (Abstract, Column 1, lines 45-67 and Claim 1). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the single-copy counting of Singer et al to the method of Bawandi et al and to detect the first and second quantum dot attached to a single copy of a target species for the expected benefit of diagnosing clinically important conditions e.g. HIV and genetic defects as taught by Singer et al (Column 3, lines 17-21).

Regarding Claim 40, Bawandi et al teach the method wherein said optical characteristic is detected by coincidence detection (Column 27, lines 26-30).

Regarding Claim 41, Bawandi et al teach the method of Claim 1 wherein said optical characteristic is fluorescence (Column 15, lines 9-49).

Regarding Claim 42, Bawandi et al teach the method of Claim 29 wherein said optical characteristic is fluorescence (Column 15, lines 9-49).

Regarding Claim 47, Bawandi et al teach the method of Claim 1 further comprising resolving the optical characteristic of the first and second quantum dot from an optical characteristic not attached to the single copy (Column 21, lines 10-31).

Regarding Claim 48, Bawandi et al teach the method of Claim 29 further comprising resolving the optical characteristic of the first and second quantum dot from an optical characteristic not attached to the single copy (Column 21, lines 10-31).

9. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bawandi et al (U.S. Patent No. 6,306,610 B1, filed 17 September 1999) and Singer et al (U.S. Patent No. 5,866,331, issued 2 February 1999) as applied to Claim 7 above and further in view of Barbera-Guillem (U.S. Patent No. 6,309,701 B1, filed 24 May 2000).

Regarding Claim 8, Bawandi et al disclose a method of detecting a target species immobilized on a substrate comprising: detecting a single copy of said target species by detecting fluorescence emitted by a quantum dot attached to said single copy, wherein said single copy is bound to an affinity moiety for said target species immobilized on said substrate (Column 22, lines 59-65) wherein said target species has distinguishable first and second quantum dot attached thereto i.e. probes labeled with two different quantum dots are attached to the nucleic acid target species via hybridization (Column 24, line 62-Column 25, line 17 and Fig. 3) and wherein said first and second dots are visually distinguishable as a first color and second color i.e. each have a distinct emission spectra (Column 4 lines 45-49) but they do not teach the first and second color combine to form a distinguishable color different from both said first and second color. However, Barbera-Guillem teach a similar method of detecting a target species comprising detecting a target species by detecting fluorescence emitted by a quantum dot attached to the target species, wherein the target species has a first and second quantum dot attached, the quantum dots having distinguishable colors which combine to form a color different (Column 2, lines 27-54) whereby targets present in minute quantities are detectable and multiple targets are distinguishable in multidimensional formats (Column 2, lines 55-66 and Column 3, lines 1-10). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the quantum dots of Bawandi et al with the combinatorial quantum dots taught by Barbera-Guillem to thereby greatly increase sensitivity and quantity of target detection of target species for the expected benefits of detecting targets present in minute quantity and distinguishing a single target in the

multidimensional format as taught by Barbera-Guillem (Column 2, lines 55-66 and Column 3, lines 1-10).

10. Claims 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bawandi et al (U.S. Patent No. 6,306,610 B1, filed 17 September 1999) and Singer et al (U.S. Patent No. 5,866,331, issued 2 February 1999) as applied to Claim 1 above and further in view of Walt et al (U.S. Patent No. 6,327,410 B1, filed 11 September 1998).

Regarding Claim 19, Bawandi et al teach a method of detecting a target species immobilized on a substrate comprising: detecting a single copy of said target species by detecting fluorescence emitted by a quantum dot attached to said single copy, wherein said single copy is bound to an affinity moiety for said target species immobilized on said substrate (Column 22, lines 59-65) wherein multiple targets are immobilized, detected and analyzed (Column 22, lines 48-67) but they do not said substrate further comprises an alignment moiety. However, alignment moieties were well known in the art at the time the claimed invention was made as taught by Walt et al Specifically, Walt et al teach a method of detecting a target species immobilized on a substrate comprising detecting a single copy of said target species by detecting emitted fluorescence wherein the target is distributed upon said substrate in a random manner (Column 4, lines 35-58) said substrate further comprising an alignment moiety (i.e. marker bead) comprising a fluorescent moiety which does not interact with said target species (Column 19, lines 2-5) wherein the alignment moiety demarks a subset of labeled targets on the substrate. Walt et al teach the demarcation allows the reuse of target labels within the same substrate thereby increasing the number of targets that can be detected on the same substrate with a minimal number of labels (Column 18, line 59-Column 19, line 5). It

would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the substrate of Bawandi et al to include the alignment moieties demarking sub-arrays as taught by Walt et al to thereby increase the number of detectable targets without increasing the number of fluorescent labels required as taught by Walt et al (Column 18, line 59-Column 19, line 5) for the obvious benefit of maximizing target detection while minimizing labeling and detection steps.

Regarding Claim 20, Bawandi et al teach the method wherein the labels are quantum dots (Column 4, lines 7-18).

Regarding Claim 21, Bawandi et al teach the labels are distinguishable (Column 4, lines 28-41) and Walt et al teach the similar method wherein the alignment moiety is distinguishable from the targets (Column 19, lines 2-5).

Regarding Claim 22, Walt et al teach the alignment moiety is correlated with the position of one or more target complexes (i.e. sub-arrays) (Column 19, lines 1-5).

Regarding Claim 23, Bawandi et al teach the method of Claim 1 comprising a substrate known in the art (Column 26, lines 15-21) but they are silent regarding the composition of the substrate. Walt et al teach the similar method wherein the substrate is e.g. glass slide, flow cell and capillary wherein their substrates minimize the amount of sample volumes required (Column 5, lines 32-60). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the substrate requiring minimal sample volumes as taught by Walt et al to the substrate in the method of Bawandi et al and to use a glass slide, capillary or flow cell for the expected benefit of economy of reagents as taught by Walt et al (Column 5, lines 55-57).

11. Claim 24, 25, 28, 32-39, 44-46 and 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bawandi et al (U.S. Patent No. 6,306,610 B1, filed 17 September 1999) and Singer et al (U.S. Patent No. 5,866,331, issued 2 February 1999) as applied to Claim 1 above.

Regarding Claim 24, Bawandi et al teach a method of detecting a target species immobilized on a substrate comprising: detecting a single copy of said target species by detecting fluorescence emitted by a quantum dot attached to said single copy, wherein said single copy is bound to an affinity moiety for said target species immobilized on said substrate (Column 22, lines 59-65) further comprising counting (i.e. quantifying) the quantum dot per unit area (i.e. each distribution) on the substrate to thereby quantifying the target species on the substrate (Column 22, lines 65-67). They do not specifically teach the quantum dot data is compared to a standard, but they teach their method is used to detect the presence and/or concentration of diagnostic-specific targets (Column 26, lines 1-6) which clearly suggest that the detected fluorescence is compared to a standard fluorescent signal diagnostic of disease because absent a known standard a diagnosis of disease could not be made. Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to compare the fluorescent signal obtained in the method of Bawandi et al to a known signal (i.e. quantum dot data) diagnostic of disease to thereby accurately diagnose the presence of disease as suggested by Bawandi et al (Column 26, lines 1-6).

Regarding Claim 25 and 28, Bawandi et al teach data obtained from the method of Claim 1 (Column 27, lines 37-56).

Regarding Claim 32, Bawandi et al teach a method of detecting a target species immobilized on a substrate and probing said first region for fluorescence emitted by a quantum dot attached to a single copy of said target species wherein said probing resolves said target species from other target species (Column 22, lines 11-26 and 59-67). Additionally they teach the method comprises defining a first region of interest (i.e. the cell) (Column 5, lines 9-17) and distinguishing a first target species (i.e. sub-cellular organelles). However, in this embodiment,

they do not specifically teach the target (i.e. the sub-cellular organelle) is immobilized on a substrate. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the immobilized target teaching of Bawandi et al to their other embodiments wherein the target comprises sub-cellular organelles and to immobilize the sub-cellular organelles (and the cells comprising the sub-cellular organelles) on the substrate to thereby assay multiple cells and/or organelles simultaneously for the expected benefit convenience and speed provided by multiplex assays as taught by Bawandi et al (Column 22, lines 59-60).

Regarding Claim 33, Bawandi et al teach the method of Claim 32 further comprising a second target species i.e. second sub-cellular organelle (Column 22, lines 11-15).

Regarding Claim 34, Bawandi et al teach the method of Claim 33 wherein the first and second region of interest are the same i.e. sub-organelles within the same cell (Column 22, lines 11-15).

Regarding Claim 35, Bawandi et al teach the method of Claim 32 wherein said probing is by two-dimensional imaging with a CCD camera (Column 27, lines 42-44).

Regarding Claim 36, Bawandi et al teach the method of Claim 32 wherein said first and second target species are different i.e. different cellular components (Column 22, lines 11-15).

Regarding Claim 37, Bawandi et al teach a method of detecting multiple target species immobilized on a substrate and probing said first region for fluorescence emitted by a quantum dot attached to a single copy of said target species wherein said probing resolves said target species from other target species (Column 22, lines 11-26 and 59-67). Additionally they teach the method comprises defining a first region of interest (i.e. the cell) (Column 5, lines 9-17) and distinguishing a first target species (i.e. sub-cellular organelles). However, in this embodiment, they do not specifically teach the target (i.e. the sub-cellular organelle) is immobilized on a substrate. However, it would have been obvious to one of ordinary skill in the art at the time

the claimed invention was made to apply the immobilized multiple targets as taught by Bawandi et al to their other embodiments wherein the target comprises sub-cellular organelles and to immobilize the sub-cellular organelles (and the cells comprising the sub-cellular organelles) on the substrate to thereby assay multiple cells and/or organelles simultaneously for the expected benefit convenience and speed provided by multiplex assays as taught by Bawandi et al (Column 22, lines 59-60).

Regarding Claim 38, the claims is drawn to a method for determining whether a target species is quantifiable by a method selected from the group selected from single target counting and ensemble counting. Bawandi et al teach a method for determining whether a target species is quantifiable by ensemble counting comprising: probing a region of interest (i.e. region comprising antibodies labeled with a different size nanocrystals) by detecting fluorescence emitted by a quantum dot attached to the target molecules immobilized on the substrate (Column 22,lines 59-67) and comparing the probing to predetermined cutoff value above which ensemble counting is used (Column 23, lines 1-8). The antibodies labeled with different size nanocrystals comprise an ensemble of immobilized labeled antibodies. Bawandi et al detects and compares the fluorescence from the labeled antibodies to thereby quantify antibodies whereby an ensemble of antibodies is quantified and wherein the ensemble is quantified only if the fluorescence is above a cutoff value i.e. above a detectable level. Bawandi et al teach probing the region of interest by detecting fluorescence emitted by a quantum dot as claimed (Column 22, lines 59-67) and they teach the location of all nanocrystals is visualized which strongly suggests they detect target density (Column 22, lines 31-33) but they do not specifically teach detecting fluorescence to determine a target species density. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the target location detection of Bawandi et al and to determine target density whereby target density would determine the number of targets within

a location because one skilled in the art would have been motivated to determine target number to thereby accurately quantify targets in a sample.

Regarding Claim 39, Bawandi et al teach detecting individual locations (Column 22, lines 31-33) and they teach detecting an ensemble of targets i.e. immobilized antibodies labeled with different size nanocrystals comprise an ensemble of labeled antibodies (Column 22, lines 65-67) but they do not teach ensemble counting on a first region and single target counting on a second region. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the counting of Bawandi et al by combining the ensemble and single target counting and to count the target species using both methods (i.e. to count the target species at a first region using ensemble counting and to count the same target species at a second region using single target counting) to thereby confirm quantity of the target species in a sample and optimize target analysis. It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Regarding Claim 44, Bawandi et al teach the method of Claim 32 wherein said optical characteristic is fluorescence (Column 15, lines 9-49).

Regarding Claim 45, Bawandi et al teach the method of Claim 33 wherein said optical characteristic is fluorescence (Column 15, lines 9-49).

Regarding Claim 46, Bawandi et al teach the method of Claim 37 wherein said optical characteristic is fluorescence (Column 15, lines 9-49).

Regarding Claims 49-51, Bawandi et al teach the method of Claims 32, 33 and 37 further comprising resolving the optical characteristic of the first and second quantum dot from an optical characteristic not attached to the single copy (Column 21, lines 10-31).

12. Claims 30, 31 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bawandi et al (U.S. Patent No. 6,306,610 B1, filed 17 September 1999) in view of Empedocles et al (Adv. Mater. 1999, 11 (15): 1243-1256): 389-396).

Regarding Claim 30, Bawandi et al teach a method of detecting a target species immobilized on a substrate comprising: detecting said target species by detecting fluorescence emitted by a quantum dot attached to said target wherein said target is bound to an affinity moiety for said target and wherein said detecting is performed using a means wherein target species are resolved (Column 22, lines 36-46) and they teach specific detection means e.g. CCD-device (Column 27, lines 42-50). Bawandi et al do not specifically teach the spacing of the target species on the substrate whereby the resolution is higher than the spacing between the targets. Empedocles et al teach resolution of single quantum dots using a CCD-device wherein the resolution is affected by environment e.g. photon coupling between quantum dots (page 1255, right column, second full paragraph, lines 3-8). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the teaching of Empedocles et al to the immobilized target complexes of Bawandi et al and using routine experimentation adjust the spacing between the complexes such that the resolution of the detection means is higher than the spacing between the complexes to thereby eliminate any negative effect resulting from photon coupling between the quantum dots as taught by Empedocles et al for the obvious benefit of optimizing experimental conditions to thereby maximize experimental results. It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Regarding Claim 31, Bawandi et al teach a method of detecting a target species immobilized on a substrate comprising: detecting a single copy of the target species by detecting fluorescence emitted by a quantum dot attached to said single copy wherein said single copy is bound to an affinity moiety for said target species thereby forming an target-

affinity moiety complex wherein said detecting is performed using a detecting means e.g. CCD-device (Column 27, lines 42-50) whereby target species are resolved (Column 22, lines 36-46) but they do not specifically teach the means has a resolution limit region whereby less than one target complex is present with the resolution region. Empedocles et al teach resolution of single quantum dots using a CCD-device wherein the resolution is affected by environment e.g. photon coupling between quantum dots (page 1255, right column, second full paragraph, lines 3-8). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the teaching of Empedocles et al to the immobilized target complexes of Bawandi et al and using routine experimentation adjust the placement of the complexes on the substrate such that the resolution region is less than the region having the target complex to thereby eliminate any negative effect resulting from photon coupling between the quantum dots as taught by Empedocles et al for the obvious benefit of optimizing experimental conditions to thereby maximize experimental results. It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Regarding Claim 43, Bawandi et al teach the method of Claim 31 wherein said optical characteristic is fluorescence (Column 15, lines 9-49).

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re*

Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-3, 5-18, 23, 29, and 30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-40 of U.S. Patent No. 6,274,323 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to methods for detecting a target molecule by detecting fluorescence emitted by a quantum dot and differ only in the patent claims being drawn to the a single species of target molecule (i.e. polynucleotide) and a single species of affinity moiety (i.e. PCR product) while the instant claims are drawn to the genus target molecule and affinity moiety. The courts have stated that a genus is obvious in view of the teaching of a species (see; In re Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989) and MPEP 2131.02). Therefore, the instantly claimed methods drawn to the genus target molecule and affinity moiety are obvious in view of the patent methods drawn to the species.

15. Claims 1-3, 5-25, 28-51 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-43 of copending Application No. 09/784,645. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to methods for detecting targets immobilized on a substrate by detecting a quantum dot and differ only in the instant claims being drawn to the genus "target" while the '645 application is drawn to species

"ligand". However, the courts have stated that genus is obvious in view of a species (see: Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). Therefore, the instantly claimed genus is obvious over the '645 species.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1-3, 5-25, 28-51 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 09/882,193. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to methods for detecting a single copy of a target comprising the step of detecting the single copy by detecting an optical characteristic of a first and second quantum dots attached to the single copy. The claims differ merely in the arrangement of the limitations e.g. instant Claims 1-39 are drawn to an immobilized target while '193 claims 6-16 are drawn to an immobilized target. The claims further differ in the instant claims are drawn to a target species while the '193 claims are drawn to a target nucleic acid. However, the '193 target is a species to the instantly claimed target genus. The courts have stated that a genus is obvious in view of the teaching of a species see Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); and In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). Therefore the instantly claimed target species (i.e. genus) is obvious in view of the '193 target nucleic acid (i.e. species).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

17. No claim is allowed.

18. The examiner's Art Unit has changed from 1655 to **1634**. Please address future correspondence to Art Unit 1634.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
February 5, 2003